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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,639	09/18/2003	Timothy Vickers	CORE0027US	4524

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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,639	VICKERS ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *108-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *108-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 5-6-08.

Claims 108-119 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 108-119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The limitations recited in claim 108, wherein each nucleoside comprises a 2'-fluoro modification in the ribo configuration, have no support in the original application as filed. These limitations first appeared in the amendments filed 5-25-06 and 5-6-08. These limitations constitute new matter and so are rejected under 35 U.S.C. 112, first paragraph.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 108-111 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of McKay et al (USPN 6,133,246), Lima et al (Biochem., Vol. 36, pages 390-398, 1997), and Elbashir et al, Cook et al (US 2007/0032446), the combination in view of Damha et al (US 2005/0142535) for the reasons of record set forth in the Office action mailed 2-6-08.

The claims are drawn to methods of eliciting cleavage of target RNA in a human or animal cell comprising contacting the cell with an oligonucleotide between 12-30 nucleotides in length, which oligonucleotide comprises a 2'-fluoro modification on each

nucleoside, and at least one, or optionally each internucleoside linkage is a phosphorothioate linkage, and which oligonucleotide comprises a 5' terminal phosphate.

Response to Arguments and Amendments

Applicant's arguments filed 5-6-08 have been fully considered but they are not persuasive. Applicant argues that the instant invention would not have been obvious to one of ordinary skill in the art for several reasons.

Applicant argues, for instance, that Damha does not teach phosphorothioate linkages, nor teaches experiments in cells, but merely looks at RNase H1 activity in a test tube. Contrary to Applicant's assertions, Damha teaches the incorporation of phosphorothioate internucleotide linkages into antisense molecules. See, e.g., page 5, paragraph 0113: "In embodiments, the internucleotide linkages of the oligonucleotides of the invention include but are not limited to...**phosphorothioate**... groups..." (emphasis added) See also claim 19, reciting phosphorothioate linkages in antisense oligonucleotides.

Applicant argues that Damha does not teach experiments in cells, but merely looks at RNase activity in a test tube. Contrary to Applicant's assertions, claims 38 and 39 clearly recite methods of inhibiting target gene expression in cells.

Applicant also argues that the instant invention would not have been obvious because it was well known at the time of the instant invention that a minimum of five consecutive DNA-like nucleosides are needed in antisense oligonucleotides to elicit target cleavage by human RNase H1, and a minimum of four consecutive DNA-like

nucleosides are needed to elicit target cleavage by *E. coli* RNase H1. Applicant additionally argues that the Elbashir article is not relevant because the present claims recite methods using single stranded compounds, and that, despite this, Elbashir shows that complete substitution of one or both of an siRNA duplex with 2'-modified nucleosides abolished RNAi activity of the duplexes. .

Contrary to Applicant's assertions, the claims do not recite the use of a particular enzyme for target cleavage, but instead, as Applicant makes clear throughout their arguments, cleavage is required to occur in a cell - and not in a test tube after the addition of a single particular enzyme such as RNase H1. And because cleavage is required to occur in cells, target gene cleavage occurs by any number of enzymes and would not be limited to RNase H1 cleavage, as implied by Applicant's arguments. It was well known in the art that cleavage occurs in cells via many mechanisms, including by uncharacterized RNases, or by RISC in the presence of single stranded antisense. See, e.g., Schwarz et al, Cell, Vol. 115, pages 199-208, 2003 on page 200, second full paragraph:

> **Single-stranded siRNA can direct RNAi** but is >10-fold less effective than siRNA duplexes, reflecting the reduced stability of single-stranded RNA in vitro and in vivo. Surprisingly, the two strands of the ... siRNA duplex, **used individually as 5' phosphorylated single-strands**, had identical rates of target cleavage...

(citations omitted) (emphasis added). See also Parrish et al, Molecular Cell, Vol. 6, pages 1077-1087, 2000, on page 1081, second full paragraph: "Modification of uracil with 2'-fluorouracil was compatible with RNAi activity..."

So, contrary to Applicant's assertions, Elbashir is properly relied upon for the routine optimization of modifications and testing the effects of these modifications on target gene cleavage in a cell using siRNA mediated cleavage. Elbashir teaches a correlation between the placement of 2'-substitutions in various positions on the oligonucleotides and the retention of siRNA mediated target gene cleavage. Elbashir teaches routine experimental approaches to test the effects of the incorporation of well known modifications on siRNA mediated cleavage, testing how these various modifications affect inhibitory activity of siRNA.

And, contrary to Applicant's assertions, the findings of Elbashir did not preclude the possibility that incorporating other types of modifications on a single strand of an siRNA molecule would retain and possibly enhance inhibitory activity. Since both the incorporation of 2'-fluoro modifications and phosphorothioate internucleotide linkages were well known to contribute to oligonucleotide stability and/or target binding, it would have been a logical scientific choice to design and test an antisense strand that is completely modified with 2'-fluoro, and optionally fully modified with phosphorothioate internucleotide linkages, to see if the advantages provided by such modifications would contribute to enhancing antisense stability and siRNA mediated activity in a cell. Applicant is again reminded that siRNA mediated cleavage was known to occur in the presence of single stranded oligonucleotides guiding the RISC complex, and that a 5' terminal phosphate group was required, as instantly claimed (see, e.g., Schwarz above).

Applicant argues that Damha does not teach antisense strands that are fully modified with 2'-fluoro groups in the ribo configuration, but instead teaches alternating motifs of 2'-modifications, including alternating 2'-fluoro modifications. Applicant is correct that Damha does not teach antisense that comprise 2'-fluoro modifications in the ribo configuration on every nucleoside. But, contrary to Applicant's assertions, the fact that Damha fails to explicitly teach the complete substitution of nucleosides with 2'-fluoro modified residues in a ribo configuration does not render the instant invention free of the prior art for several reasons.

The combined teachings of McKay, Elbashir, Lima, Cook and Damha, and not the complete reliance on the teachings of Damha, indeed render the instant invention obvious. McKay teaches compositions comprising antisense oligonucleotides between 8 and 50 nucleobases in length which optionally comprise phosphorothioate internucleotide linkages and 2'-fluoro sugars, and their ability to inhibit target gene expression inhibition using routine methods of modifying antisense and using routine screening of modulators comprising various configurations of modifications for their ability to target and inhibit expression of mRNA in cells. Lima teaches methods of modifying oligonucleotides, including incorporating phosphorothioate internucleotide linkages and 2'-fluoro-modified sugars into oligonucleotides, and determining the effects of incorporating these modifications, in various configurations, on the stability of oligonucleotides from degradation, and on the effect of various configurations of phosphorothioate and 2'-fluoro- modifications on the oligonucleotides on their binding affinity and rates of catalysis. Elbashir provides a rational approach to the routine

optimization of siRNA molecules for eliciting target mRNA cleavage, including the testing of incorporation of routine oligonucleotide modifications for siRNA optimization. Cook teaches methods of modifying oligonucleotides, including incorporating phosphorothioate internucleotide linkages and 2'-fluoro-modified sugars into oligonucleotides, and determining the effects of incorporating these modifications, in various configurations, on the binding affinity and rates of catalysis. Damha teaches the routine incorporation of modified residues into oligonucleotides, including 2'-modifications such as fluoro-, deoxy, alkoxy groups, and at least one or optionally each linkage is a phosphorothioate internucleotide link, or which modifications occur in various configurations and patterns, and which oligonucleotides are between 12-30 nucleotides in length, and comprise a 5' terminal phosphate. Damha teaches the routine testing of these variously modified oligonucleotides for their ability to elicit target gene cleavage in human or animal target cells.

So, relying on the combined teachings of McKay, Lima, Elbashir, Cook and Damha, it would have been obvious to screen various antisense oligonucleotide molecules for their ability to elicit cleavage of a known target gene in a cell, either through an siRNA or RNase mechanism, and which oligonucleotides comprise various modifications and configurations, including those instantly claimed, because it was well known in the art, as taught by McKay et al, Lima et al, Elbashir et al, Cook et al and Damha et al, that the incorporation of various modifications including incorporation of 2'-O or 2'-Fluoro modifications, phosphorothioates, enhance oligonucleotide stability,

and/or target binding and target gene cleavage, and the particular configuration would require routine screening as taught previously by these references.

It has been standard operating procedure for laboratories to design modifications in various configurations for antisense oligonucleotides, then assay them for stability, target binding and eliciting siRNA or RNase cleavage, as taught previously by many in the art, including McKay et al, Lima et al al, Elbashir et al, Crooke et al, Cook et al and Damha et al. One of ordinary skill in the art would have expected that the incorporation of these modifications would provide for either higher affinity for a target gene, enhanced oligonucleotide stability from non-specific nucleases, and/or enhanced cleavage of target genes, and to test for optimal configurations would be routine experimentation to one of ordinary skill in the art, including the incorporation of nucleosides, all of which comprise 2'-fluoro modifications and in a ribo configuration.

For these reasons, the instant rejection is maintained.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
7-28-08

/Jane Zara/

Primary Examiner, Art Unit 1635